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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/982,548	LIU ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,42,43,58,59,73,79,82,89-91,99 and 113-140* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,42,43,58,59,73,79,82,89-91,99 and 113-140* is/are rejected.

7)☒ Claim(s) *38,42 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed August 29, 2003 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 113-140 have been added.

An action on the merits of claims 1-38, 42-43, 58-59, 73, 79, 82, 89-91, 99, and 113-140 is contained herein below.

Election/Restrictions

Applicant's election of species of group 1A in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that applicants have elected species A1 wherein the diseases to be treated are coagulation disorders which are contingent upon anti-coagulant activity. However, upon further review, it appears that the instant application is drawn to a new way of delivering polysaccharides in which the novelty lies in the size of the particle administered. The diseases which are to be treated are each known in the art to be effectively treated by the polysaccharides, thus, the examiner has withdrawn the species requirement and will examine all claims currently pending.

Information Disclosure Statement

The information disclosure statement filed 1/30/2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. It is noted that the references listed on the IDS are not with the file.

Claim Objections

Applicant is advised that should claim 1 be found allowable, claims 38, 42, and 58 will be objected to under 37 CFR 1.75 as being a substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claim 1 is drawn to "a method of producing a therapeutic effect comprising: administering to the pulmonary tissue of a subject an unformulated dry polysaccharide particle in an effective amount for producing a therapeutic effect, wherein the unformulated dry polysaccharide particle has a mean geometric diameter of 1-500 microns". Claim 38 is drawn to a method of delivering at least 5% of a polysaccharide to the lower respiratory tract comprising the step of administering to the pulmonary tissue of a subject an unformulated dry polysaccharide particle, wherein the unformulated dry polysaccharide particle has a mean geometric diameter of 1-500 microns, and wherein at least 5% of the polysaccharide is delivered to the lower respiratory tract. Claim 42 is drawn to a method of systemically delivering a polysaccharide to a subject comprising the step

of administering to the pulmonary tissue of a subject an unformulated dry polysaccharide particle, wherein the unformulated dry polysaccharide particle has a mean geometric diameter of 1-500 microns. Claim 58 is drawn to a method of delivering a glycosaminoglycan to a subject comprising the step of administering to the pulmonary tissue of a subject an unformulated dry glycosaminoglycan particle having a mean geometric diameter of 1-500 microns. These claims are seen to be duplicates of each other, wherein the only active step in each claim is administering to the pulmonary tissue of a subject an unformulated dry polysaccharide particle, wherein the unformulated dry polysaccharide particle has a mean geometric diameter of 1-500 microns.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-37, 42, 58-59, 73, 79, 82, 89-91, 99, and 116-140 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite wherein the claim is drawn to "a method for producing a therapeutic effect, comprising: administering to a pulmonary tissue of a subject an unformulated dry polysaccharide particle in an **effective amount** for producing a therapeutic effect...". The term "effective amount" is indefinite where the claim fails to state the function which is to be rendered effective. See ***In re Frederiksen, 102 USPQ 35 (CCPA 1954).*** Moreover, it is unclear as to what

applicants intend by the recitation of an "unformulated polysaccharide". Clarity is respectfully requested.

The term "low molecular weight heparin" in all instances, such as in claim 5, is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Defining what is intended by "low molecular weight" in the claim, would be seen to obviate the rejection at hand.

The recitation in a dependent claim of the source of an active agent to be used in a method from which said claim depends, wherein the "source of the active agent" does not result in a patentably distinguishable methodological and manipulative difference in how said active agent's source impacts the method from which it depends, renders the claim(s) in which it occurs and which depend therefrom indefinite for failing to distinctly articulate how such a recitation further limits the method from which said dependent claim(s) applicant regards as the invention. In the instant case, claim 6 provides that "wherein the heparin is a biotechnology derived heparin", and it is unclear how the method of making the heparin will effect the method of using the heparin.

The phrase, "a chemically modified heparin" is indefinite. The claim does not set forth how the heparin is modified, and to what extent the heparin is modified. Heparin is an art known compound which can be modified in a multitude of ways. In the absence of the identity of moieties which are intended to modify the art recognized chemical core, described structurally or by chemical name, the identity of "a modified heparin" would be difficult to ascertain. In the

absence of said moieties, the claims containing the term "modified" are not described sufficiently to distinctly point out that which applicant intends as the invention.

Claim 9 is indefinite wherein the claim provides that the heparin analogue of claim 8 is optionally an oligosaccharide, wherein the heparin analogue of claim 8 is a glycosaminoglycan of claim 2 and the glycosaminoglycan of claim 2 is the polysaccharide of claim 1. It is unclear how the polysaccharide of claim 1 can be further limited to an oligosaccharide of claim 9.

Claim 10 is indefinite wherein the claim provides that the glycosaminoglycan is an "unfractionated heparin preparation". It is unclear by what is intended by an "unfractionated heparin preparation".

Claim 32 is indefinite wherein the claim provides that the polysaccharide is optionally a pectin "derivative". In the absence of the identity of moieties intended to modify an art recognized chemical core, described structurally or by chemical name, the identity of a "derivative" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "derivative" are not described particularly sufficiently to distinctly point out that which applicant intends as the invention.

Claim 43 is indefinite wherein the claim is drawn to "a composition consisting of unformulated dry glycosaminoglycan having a mean geometric diameter of 1-500 microns". However, a composition must contain two things, i.e., a compound and a carrier. It is unclear how a composition can consist of only 1 agent. Moreover, this claim uses closed language such as "consisting of". Claim 122 further limits claim 43 by adding an additional agent to the composition. It is unclear how there can be an additional agent added if the composition uses closed language.

The term "rapidly" or "rapid" in claims 59, 73, and 79 are relative terms which render the claims indefinite. The terms are not defined by the claim, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Clarity is respectfully requested.

The phrase "heparin-like glycosaminoglycan" in claims 82, 89, and 90 is a relative term which renders the claims indefinite. The term is not defined by the claims, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Clarity is respectfully requested.

Claim 91 is indefinite wherein the claim is drawn to a kit comprising an inhalation apparatus, a polysaccharide, and a detection system. It is unclear as to what exactly a "detection system" is. There is nothing in the claim about detecting anything, and it is unclear as to what the "detection system" is included in the kit for.

All claims which contain the terms "unformulated" glycosaminoglycan" or a "formulated" glycosaminoglycan, as in claim 99 for example, are indefinite. It is unclear as to what is intended by a formulated or an unformulated glycosaminoglycan, polysaccharide, or heparin.

Claims 121 and 123 are indefinite as they contain terms which are indefinite for various reasons as set forth supra, for example, "a low molecular weight heparin", "a chemically modified heparin", "an unfractioned heparin preparation", etc.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43 and 118 are rejected under 35 U.S.C. 102(b) as being anticipated by Platz et al. WO 96/32149).

Claim 43 is drawn to a composition consisting of unformulated dry glycosaminoglycan having a mean geometric diameter of 1-500 microns. Claim 118 limits the size to 1-5 microns.

Platz et al. teach a heparin composition with particles having a diameter of 3.5 microns (example IX).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determining the scope and contents of the prior art.

Ascertaining the differences between the prior art and the claims at issue.
Resolving the level of ordinary skill in the pertinent art.
Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-38, 42-43, 58, and 113-115 rejected under 35 U.S.C. 103(a) as being unpatentable over Sackner et al. (US Patent 4,679,555) in view of the combination of Edwards et al. (WO 98/31346), and Platz et al. (WO 96/32149).

Claim 1 of the instant application is drawn to a method of producing a therapeutic effect comprising administering to a pulmonary tissue an unformulated dry polysaccharide particle which has a mean geometric diameter of 1-500 microns. Claim 2 limits the polysaccharide to a glycosaminoglycan (GAG), and claims 3-10 limit the GAG to various heparins. Claims 11-14 limit the mean geometric diameter to various ranges. Claim 15 limits the particles mean aerodynamic diameter to 1-5 microns. Claim 16 limits the mean aerodynamic diameter to either 5-35 microns or 35-75 microns. Claims 17-31 and 35 are drawn to various conditions which are to be treated which are all art recognized heparin treated diseases. Claim 32 provides various polysaccharides which may be used. Claim 33 provides that the polysaccharide is self-administered, and claim 34 provides it is administered through the tracheal tube. Claim 36 provides that the tap density is in the range of 0.01-0.4 g/cm^3 and claim 37 provides that the tap density is greater than 0.4 g/cm^3. Claims 38, 42, and 58 are seen to be substantial duplicates of claim 1, as set forth supra. Claims 113-115 provide that 10%, 30%, or 50% of polysaccharide administered is delivered to the lower respiratory tract.

Sackner et al. teach of a method of utilizing a metered dose inhaler (MDI) with an inhalation device to improve the efficiency with respect to the amount of heparin reaching the lungs of a patient. Sackner teach that by utilizing the MDI, the standard large size particles which

normally are deposited on the mucosa of the mouth and throat are no longer present, but rather the particles which enter the patient's mouth are essentially pure medicament and of such small size, that greater numbers of the particles can be completely inhaled into the lungs (column 4, lines 43-56). Sackner et al. additionally teach therapeutic uses of heparin which are correlative to that of the instant application (column 1, line 16 – column 12, line 55). What is not taught by Sackner et al. is to administer particles which have the specific diameters and tap densities as set forth in applicant's claims.

Platz et al. teach of various pulmonary deliverable aerosolized medicaments which have specific properties for inhalation. Platz et al. teach the mass median diameter (which is seen to be the same as the mean geometric diameter) to be about 1.0-5.0 microns and a mass median aerodynamic diameter of about 1.0-5.0 microns (pages 3-4). Moreover, Platz et al. teach that heparin can be used as the drug (page 5).

Edwards et al. teaches of preparations of particles for inhalation wherein the particles for inhalation have properties comprising: a mass mean diameter of between 5-30 microns, a tap density of less than about 0.4 g/cm^3, and an aerodynamic diameter of the particles is between 1-3 microns are used (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a preparation of particles for inhalation with the properties as set forth by Edwards and Platz using heparin as disclosed by Sackner because Sackner teach that heparin is not absorbed by the GI tract and thus cannot be administered orally and Platz teaches heparin to be used in their aerosols. One would be motivated to administer a heparin with the claimed features to a patient because the claimed features are taught to be acceptable for particles which are to be

administered via pulmonary delivery. That is, Edwards and Platz teach that particles for delivery to the pulmonary cavity should have a tap density of about 0.4 g/cm^3, an aerodynamic diameter of about 1-5 microns, and a mass mean diameter of about 5-30 microns. Platz et al. indeed contemplates the use of heparin, and Sackner teaches heparin should be delivered via an aerosol. Additionally, one of ordinary skill in the art would be able to optimize the method and the particles to obtain a composition which provides various percentages of the polysaccharide to the lower respiratory tract and would be motivated to do so because the prior art teaches that particles which are too small are sometimes not deposited in the lungs and are exhaled, and particles which are to big can deposit on the mucous membrane of the trachea rather than in the lower respiratory tract.

Claims 59, 73, 79, and 130-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sackner et al. (US Patent 4,679,555) in view of the combination of Edwards et al. (WO 98/31346), and Platz et al. (WO 96/32149) as applied to the claims above.

Claims 59, 73, and 79 are drawn to methods of rapidly delivering a polysaccharide to a subject by administering a dry aerosol containing a polysaccharide to a subject wherein either a peak plasma concentration occurs within two hours or wherein at least 5% of the polysaccharide is delivered within one hour. Claims 130-134 state various percentages of the polysaccharide which is delivered to the blood within one hour.

Sackner et al. teach of a method of utilizing a metered dose inhaler (MDI) with an inhalation device to improve the efficiency with respect to the amount of heparin reaching the lungs of a patient. Sackner teach that by utilizing the MDI, the standard large size particles which normally are deposited on the mucosa of the mouth and throat are no longer present, but rather

the particles which enter the patient's mouth are essentially pure medicament and of such small size, that greater numbers of the particles can be completely inhaled into the lungs (column 4, lines 43-56). Sackner et al. additionally teach therapeutic uses of heparin which are correlative to that of the instant application (column 1, line 16 – column 12, line 55). What is not taught by Sackner et al. is to administer polysaccharides via a dry aerosol to obtain the claimed results in the time frames specified.

Platz et al. teach of various pulmonary deliverable dry aerosolized medicaments which have specific properties for inhalation. Moreover, Platz et al. teach that heparin can be used as the drug (page 5).

Edwards et al. teaches of preparations of particles for inhalation which have improved aerosolization properties wherein the particles for inhalation have properties comprising: a mass mean diameter of between 5-30 microns, a tap density of less than about 0.4 g/cm^3, and an aerodynamic diameter of the particles is between 1-3 microns are used (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to test the particles above and determine the time frame for release of a specific drug to be delivered because it is known that various drugs require a rapid delivery, and others require a delayed release delivery. The method of producing a dry aerosol of heparin is indeed taught in the prior art, merely stating the properties in which the product is released is seen to be a result of the physical characteristics of the composition itself, which as set forth supra, would have been obvious to one of ordinary skill in the art with the above references before them.

Claims 43, 82, 89, 90, 116-129, and 135-140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sackner et al. (US Patent 4,679,555) in view of the combination of Edwards et al. (WO 98/31346), and Platz et al. (WO 96/32149) as applied to the claims above.

The claims of the instant application are drawn to compositions comprising a glycosaminoglycan with a particle size of various ranges within 1-500 microns, wherein the particles have a mean aerodynamic diameter of greater than 5 microns, and wherein the tap density of the particles is greater than 0.4 g/cm^3. Moreover, claim 121 limits the glycosaminoglycan to various products, including heparin. Claim 122 provides there is a formulated and unformulated glycosaminoglycan in the preparation. Claim 123 limits the formulated GAG to optionally heparin. Claims 124 and 125 provide that the formulated and unformulated GAG's are either the same or different. Claims 126 and 140 provide that the formulated GAG includes a polymer to effect slow release. Claim 127 limits the polymer to PLA, PGA, or PLGA. Claims 128 and 139 provide there is additionally a surfactant, and claim 129 limits the surfactant to DPPC. Claims 135 and 136 limit the particles to either of spherical or non-spherical. Claims 137 and 138 limit the composition to either porous or non-porous.

Sackner et al. teach of compositions utilizing a metered dose inhaler (MDI) with an inhalation device to improve the efficiency with respect to the amount of heparin reaching the lungs of a patient. Sackner teach that by utilizing the MDI, the standard large size particles which normally are deposited on the mucosa of the mouth and throat are no longer present, but rather the particles which enter the patient's mouth are essentially pure medicament and of such small size, that greater numbers of the particles can be completely inhaled into the lungs (column 4, lines 43-56). Sackner et al. additionally teach therapeutic uses of heparin which are correlative to

that of the instant application (column 1, line 16 – column 12, line 55). What is not taught by Sackner et al. is the composition with the various properties.

Platz et al. teach of various pulmonary deliverable aerosolized medicaments which have specific properties for inhalation. Platz et al. teach the mass median diameter (which is seen to be the same as the mean geometric diameter) to be about 1.0-5.0 microns and a mass median aerodynamic diameter of about 1.0-5.0 microns (pages 3-4). Moreover, Platz et al. teach that heparin can be used as the drug (page 5).

Edwards et al. teaches of preparations of particles for inhalation wherein the particles for inhalation have properties comprising: a mass mean diameter of between 5-30 microns, a tap density of less than about 0.4 g/cm^3, and an aerodynamic diameter of the particles is between 1-3 microns are used (abstract). Edwards teaches surfactants which can be used which are correlative to those of the instant application (page 11) and polymers which can be used for different controlled drug deliver application(page 10)

Compositions for aerosol delivery of an active agent are known in the art to comprise particles which have the same dimensions as those claimed in the instant application. Heparin is taught to be utilized in the dry aerosol particulate compositions of the prior art because of acceptable delivery of the product in an area wherein the product is not degraded (as in the acidic pH of the lumen of the gut). The methods of treatment utilizing the compositions are shown to be obvious over the prior art as set forth supra, therefor the composition utilized in the methods would be obvious over the prior art documents and one would be motivated to make the compositions to be able to administer them in they methods. Moreover, the fact that applicants claim the particles to be either spherical or non-spherical and porous or nonporous, shows that

these are not necessarily essential elements to the invention, but some possible forms of the particles which can be used.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
November 5, 2003